REMARKS

Claims 9-23 were pending in the application. Claims 9-18 are canceled without prejudice or disclaimer. Claim 19 is amended to recite applicants invention more clearly. Claims 24-29 are added to recite specific embodiments of the invention. Support for these claims is found throughout the specification and in prior claims 9-14. Applicants respectfully request entry of these amendments, which are fully supported by the as-filed specification, and reconsideration of claims 19-29. For the Examiner's convenience, the claims that will be pending upon entry of this amendment are set forth in the attached Appendix.

Formal Matters

The specification was objected to for failing to reflect the priority information of the application. The specification has been amended to obviate this objection. Applicants also have amended the specification to claim priority to co-pending U.S. application Serial No. _____, filed February 21, 1997, which is a file-wrapper continuation of 08/268,520, filed June 30, 1994. (Applicants do not yet have a serial number for the FWC. A copy of the post card indicating receipt of the FWC by the Patent Office on February 21, 1997, is attached.) This prior application discloses a method of treating chronic rheumatoid arthritis using an anti-IL-6 receptor antibody, and has a common inventor with the instant application, Tadamitsu Kishimoto. A substitute declaration claiming priority to this application is attached. A claim for priority to the Japanese application to which 08/268,520 claims priority and are English translation of this application also are attached.

The specification was objected to for lacking an Abstract. An Abstract is submitted herewith on a separate sheet.

The claims were objected to for not forming a complete sentence. Applicants have amended the first page of the claims

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to begin with "What is claimed is," as suggested at page 2 of the Action.

Rejections Under 35 USC § 112, First Paragraph

Claims 10 and 19-23 were rejected for an alleged lack of enablement. Claim 10 was canceled, but instant claim 25 roughly corresponds to canceled claim 10. Claims 19-23 and 25 recite *in vivo* methods of inhibiting synovial cell growth. The Examiner questions whether the *in vitro* and murine data reported in the specification demonstrate the ability of the claimed methods to inhibit synovial cell growth *in vivo*.

The Examples set forth in the specification demonstrate that the administration of an anti-IL-6 antibody or an anti-IL-6 receptor antibody inhibits synovial cell growth *in vivo*. Although Example 1 is an *in vitro* experiment where the cells were not subjected to growth inducing cytokines present *in vivo*, this experiment nevertheless demonstrates the ability of an anti-IL-6 antibody or an anti-IL-6 receptor antibody to inhibit synovial cell growth. Complete inhibition of synovial cell growth was observed in cells treated with an anti-IL-6 antibody or an anti-IL-6 receptor antibody, while no inhibition of synovial cell growth was observed in cells receiving no antibody. These results demonstrate that the inhibition of synovial cell growth is due to the administered anti-IL-6 or anti-IL-6 receptor antibodies.

Example 2 is an *in vivo* experiment in a mouse arthritis model. This example demonstrates that the *in vivo* administration of an anti-IL-6 receptor antibody inhibits synovial cell growth. Onset of arthritis from early stage arthritis was suppressed in the anti-IL-6 receptor antibody-treated group compared to the control group, which received an anti-DNP antibody of the same isotype. The Action recognizes that swelling was reduced in the antibody-treated mice, but questions whether this effect is

attributable to the inhibition of synovial cell growth. Applicants respectfully point out the other evidence of inhibition of synovial cell growth reported in this example:

When the cartilage and bone of the treated mice were analyzed, it was discovered that the invasion of granulation tissue into the cartilage and bone was suppressed in the anti-IL-6 receptor antibody-treated group compared to the control group. See page 24, lines 18-29, of the specification. This suppression of the invasion of granulation tissue indicates that synovial cell growth was inhibited.

Although applicants believe that the examples in the specification fully enable the claims at issue, applicants are submitting a Declaration of Masahiko Miharo, an inventor of the application, which further evidences the enablement of the claimed invention. Applicants respectfully request that this Declaration be considered by the Examiner and made of record in the application.

The Declaration sets forth data from two experiments. Experiment 1 demonstrates that the administration of an anti-IL-6 receptor antibody suppressed the onset of collagen-induced arthritis in monkeys. The administration of an anti-IL-6 receptor antibody almost completely suppressed arthritis and also suppressed synovial cell growth compared to a control group receiving no antibody, in which clinical signs of arthritis and synovial cell growth were observed. This experiment demonstrates the ability of an anti-IL-6 receptor antibody to suppress arthritis and suppresses synovial cell growth *in vivo*, in the presence of other cytokines.

Experiment 2 demonstrates that the administration of an anti-IL-6 receptor antibody to a monkey almost completely inhibits the increase in C-reactive protein (CRP) induced by the

administration of IL-6, as compared to a control group receiving no antibody. This experiment demonstrates the ability of an anti-IL-6 receptor antibody to inhibit IL-6 activity *in vivo*, in the presence of other cytokines.

The data set forth in this Declaration, together with the data in the specification, evidence that the present invention can effectively inhibit synovial cell growth *in vivo*. Because someone skilled in the art can practice the invention recited in claims 19-23 and 25 without an undue amount of experimentation, the requirements of §112, first paragraph, are met, and this rejection should be withdrawn.

Rejections Under 35 USC § 102

Claims 9 and 17 were rejected under §102 as allegedly being anticipated by U.S. Patent No. 5,591,827. The cancellation of these claims obviates this rejection.

Rejections Under 35 USC § 103

Claims 9 and 17-18 were rejected under §103 as allegedly being obvious in view of U.S. Patent No. 5,591,827. The cancellation of these claims obviates this rejection.

Claims 9 and 11-18 were rejected under §103 as allegedly being obvious in view of U.S. Patent No. 5,591,827, Sipe, U.S. Patent No. 5,559,012, and Hirata. Claims 9 and 11-18 have been canceled. Applicants respectfully traverse these rejections in as much as they may be applied to instant claims 24-29.

At the outset, applicants point out that Sipe and U.S. Patent No. 5,559,012 are not prior art against the instant claims. This application was filed April 7, 1997, as a national stage of a PCT application filed June 7, 1995, which claims priority to a Japanese application filed October 7, 1994 (JP 6-244035). This application also claims priority to U.S.

application Serial No. 08/268,520, filed June 30, 1994, which claims priority to two Japanese applications filed July 21, 1993 (JP 5-180303) and August 25, 1993 (JP 5-210570), respectively.

Sipe was published in April of 1994. This is after July 21 and August 25, 1993, the filing dates of JP 5-180303 and JP 5-210570, to which this application claims priority through 08/268,520. JP 5-180303 and JP 5-210570 evidence that applicants invented the invention recited in claims 24 and 26-28 prior to the publication of Sipe. Because 08/268,520 was filed less than one year after Sipe was published, Sipe is not a §102(b) bar against the instant application. Accordingly, Sipe is not prior art against these claims.

U.S. Patent No. 5,559,012 has a §102(e) date of July 25, 1994. This is after June 30, 1994, the filing date of 08/268,520. 08/268,520 evidences that applicants invented the invention recited in claims 24 and 26-28 prior to the filing date of this patent; accordingly, this patent is not prior art against these claims.

Applicants also point out that the cited references do not establish the prima facie obviousness of the instantly recited methods of treating chronic rheumatoid arthritis. Claims 24-29 recite methods of treating chronic rheumatoid arthritis comprising administering an anti-IL-6 receptor antibody. This invention is not taught or suggested by the cited references.

U.S. Patent No. 5,591,827 is directed to IL-6 muteins which act as IL-6 receptor agonists and inhibit normal IL-6 activity. As recognized at page 5 of the Action, there is no teaching or suggestion in this reference of using an anti-IL-6 receptor antibody to treat chronic rheumatoid arthritis as presently claimed.

Sipe was cited for teaching "that the destruction of joints caused by rheumatoid arthritis is due in part to the action of . . . cytokines such as IL-1 and IL-6." Action, page 5. It is important to note, however, that Sipe does not teach or suggest that IL-6 ***causes*** rheumatoid arthritis. In fact, Sipe states that "[t]he exact role of IL-6 in arthritic synovium has not yet been clearly defined." Sipe, page 246.

Sipe teaches that although IL-6 detrimentally inhibits proteoglycan synthesis, "it does not appear to influence production of the metalloproteases." Sipe, page 248. Moreover, Sipe teaches that because IL-6 "appears to stimulate the production of TIMP," it "would counteract the degradative potential of IL-1." Sipe, page 248. These teachings suggest that one might not want to inhibit IL-6 activity because IL-6 has an apparent beneficial effect. Accordingly, Sipe teaches away from the present invention.

Although the abstract of Sipe generically states that "anti-cytokine receptor antibodies" are potential agents for cytokine reduction, Sipe does not teach or suggest that anti-IL-6 receptor antibodies might be useful in treating chronic rheumatoid arthritis. Instead, Sipe teaches that the "[p]harmacologic regulation of IL-1 and TNF-α" are the "primary targets for treatment of arthritis." The fact that Sipe focuses on these two cytokines instead of IL-6 is further evidence that Sipe teaches away from the present invention.

U.S. Patent No. 5,559,012 was cited for teaching a pharmaceutical composition comprising anti-IL-6 antibodies. This reference does not teach or suggest a pharmaceutical composition comprising an anti-IL-6 receptor antibody, and in fact teaches away from such a composition at column 1, lines 36-41. Moreover, there is no teaching or suggestion in this reference that an

anti-IL-6 receptor antibody might be useful in treating chronic rheumatoid arthritis, as presently claimed.

Hirata was cited for teaching a monoclonal IL-6 receptor antibody. There is no teaching or suggestion in this reference that such an antibody might be useful in the treatment of chronic rheumatoid arthritis, as presently claimed.

In summary, the cited references fail to teach or suggest the invention recited in claims 24-29. The assertion that someone skilled in the art "would have been motivated to combine the references with a reasonable expectation of success" in view of the teachings of Sipe is entirely based on impermissible hindsight. As discussed above, there is no teaching or suggestion in Sipe that IL-6 causes chronic rheumatoid arthritis or that the use of anti-IL-6 receptor antibodies might effectively treat chronic rheumatoid arthritis. In fact, as pointed out above, Sipe teaches away from the claimed method.

"To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03 (citing *In re Royka*, 180 USPQ.2d 580 (CCPA 1974). Here, where the cited references do not teach or suggest that an anti-IL-6 receptor antibody might be effective in treating chronic rheumatoid arthritis, and where it is only ***applicants' specification*** which provides this teaching, the §103 rejection is improper and should be withdrawn.

At the time of the present invention, the pathogenic mechanism of rheumatoid arthritis was not known. It was (and still is) believed that various cytokines are involved in the pathogenesis of rheumatoid arthritis. See Sipe and HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 1440-41, Wilson *et al.* eds. (1991) (teaching eleven cytokines that play a role in chronic rheumatoid

arthritis), a copy of which is attached for the Examiner's convenience.

At the time of the present invention, it also was completely unclear whether IL-6 caused rheumatoid arthritis, whether a high level of IL-6 worsened rheumatoid arthritis, or whether a high level of IL-6 was a mere indication of rheumatoid arthritis. Although Sipe indicates that IL-6 is associated with the ***symptoms*** of rheumatoid arthritis, this in no way suggests that there is a ***causal*** relationship between IL-6 and rheumatoid arthritis. In fact, it was believed that a high level of IL-6 was induced by an inflammation reaction that was not specific to rheumatoid arthritis because IL-6 production is increased in many other diseases. *See* Sipe and Miyasaka *et al.*, *Clin. Immunol. and Immunopath.* 52: 238-47 (1989) (reporting increased IL-6 production in rheumatoid arthritis, psoriatic arthritis and Bechet's disease); Houssiau *et al.*, *Arthritis and Rheum.* 31(6): 784-88 (1988) (reporting increases in IL-6 activity in patients with infectious diseases of the central nervous system and in patients with noninfectious inflammatory condition), copies of which are attached for the Examiner's convenience. Thus, prior to the present invention, it was not known that IL-6 was involved in worsening the symptoms of rheumatoid arthritis.

The present invention is both surprising and unexpected in view of the prior art. Prior to the present invention, it was believed that an anti-inflammatory action provided by IL-6 was effective for treating rheumatoid arthritis. See Sipe and Mihara *et al.*, *Eur. J. Immunol.* 21: 2327-2331 (1991) (noting the anti-inflammatory activity of IL-6); Wendling *et al.*, *J. Rheum.* 20: 259-62 (1993) (noting the anti-inflammatory activity of IL-6); Aderka *et al.*, *J. Immunol* 143: 3517-23 (1989) (finding that IL-6 inhibits TNF production); Schindler *et al.*, *Blood* 75: 40-47 (1990) (finding that IL-6 inhibits IL-1 and TNF production); Tilg *et al.*, *Blood* 83: 113-18 (1994) (finding that IL-6 has anti-

inflammatory activity and stimulates IL-1 and TNF antagonists); Sato *et al.*, *Biochem. Biophys. Res. Comm.* 170: 824-29 (1990) (finding that IL-6 stimulates production of TIMP); Naitoh *et al.*, *Biochem. Biophys. Res. Comm.* 155: 1459-63 (1988) (finding that IL-6 increases production of ACTH). Copies of these references are attached for the Examiner's convenience. These references demonstrate that prior to the present invention those skilled in the art did not expect that ***blocking*** IL-6 activity (for example, through the use of anti-IL-6 receptor antibodies) would be an effective method of treating chronic rheumatoid arthritis because it was believed that IL-6 might play a role in ***alleviating*** the symptoms of rheumatoid arthritis.

Experiment 2 of the attached Declaration evidences another surprising and unexpected aspect of the present invention. As discussed above, this experiment demonstrates that an anti-IL-6 receptor antibody almost completely suppresses the increase in CRP induced by the administration of IL-6. Prior to the present invention, it was believed that CRP had anti-inflammatory activity. *See* Kew *et al.*, *J. Lab. Clin. Med.* 115: 339-45 (1990), a copy of which is attached for the Examiner's convenience. Instead, applicants have demonstrated that the administration of an anti-IL-6 receptor antibody both inhibits CRP and reduces inflammation. These findings are surprising and unexpected in view of the prior art, and are evidence of the nonobviousnes of the invention. *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966).

The present invention satisfies a long-felt need in the art for an effective method of treating chronic rheumatoid arthritis. Sasai *et al.*, Saishin Igaku 51: 2373-77 (1996) reports dramatic therapeutic results achieved with the administration of a humanized anti-IL-6 receptor antibody to humans suffering from rheumatoid arthritis that had proven resistant to DMAD (disease modifying antirheumatic drug). A copy of this article and an

English translation thereof are attached for the Examiner's convenience. As reported in this article, anti-IL-6 receptor antibody therapy proved effective where other methods of treatment had failed. These results demonstrate the significant benefit this invention offers over prior art methods of treating chronic rheumatoid arthritis, and are further evidence of the nonobviousness of the invention. *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966).

Conclusion

In view of the foregoing amendments and remarks, applicants believe that the application is in condition for allowance, and an early notice to this effect is earnestly solicited. Should there be any questions regarding this application, or should any issues remain, Examiner VanderVegt is invited to contact the undersigned agent of record at the telephone number set forth below.

It is believed that no additional fees are required; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.

It is further believed that no additional petition for an extension of time under 37 C.F.R. § 1.136 is required. However, should such a petition be required, applicants hereby petition the Commissioner for an extension of time, and authorize the Commissioner to charge the necessary petition fee to Deposit Account No. 19-0741.

Respectfully submitted,

January 22, 1998
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Appendix: Pending Claims

19. A method for inhibiting synovial cell growth, comprising administering to a patient in need thereof a pharmaceutical composition comprising an interleukin-6 antagonist and a physiologically acceptable carrier.

20. The method according to claim 19, wherein the interleukin-6 antagonist is selected from the group consisting of an interleukin-6 antibody and an interleukin-6 receptor antibody.

21. The method according to claim 20, wherein the antagonist is a monoclonal antibody.

22. The method according to claim 19, wherein the patient is a human.

23. The method according to claim 22, wherein the antagonist is administered in four divided doses of from about 1 to 1000 mg.

24. A method of treating chronic rheumatoid arthritis, comprising administering to a patient in need thereof a pharmaceutical composition comprising an antibody against an interleukin-6 receptor and a physiologically acceptable carrier.

25. The method according to claim 24, wherein the antibody suppresses abnormal growth of synovial cells.

26. The method according to claim 24, wherein the antibody is an antibody against a human interleukin-6 receptor.

27. The method according to claim 24, wherein the antibody is a monoclonal antibody.

28. The method according to claim 24, wherein the patient is a human.

29. The method according to claim 28, wherein the antibody is administered in four divided doses of from about 1 to 1000 mg.

Abstract of the Disclosure

Methods for inhibiting synovial cell growth and treating chronic rheumatoid arthritis are provided. The methods comprise administering a pharmaceutical composition comprising an interleukin-6 antagonist, such as an anti-IL-6 receptor antibody, and a physiologically acceptable carrier.